Coexisting primary hyperparathyroidism and Albright's hereditary osteodystrophy – an unusual association

Haruka Sasaki¹, Nobutaka Tsutsu¹, Takashi Asano¹, Takashi Yamamoto¹, Masahiro Kikuchi² and Makoto Okumura¹

Departments of ¹Internal Medicine and ²Pathology, Fukuoka University School of Medicine, Fukuoka, Japan.

Summary: Primary hyperparathyroidism associated with Albright's hereditary osteodystrophy was diagnosed in a 22 year old Japanese woman, the second such case to be reported. Albright's hereditary osteodystrophy (AHO) appears to be associated with a larger number of disorders than the well recognized pseudohypoparathyroidism. AHO and pseudo-pseudohypoparathyroidism are essentially identical.

Introduction

The clinical syndrome characterized by short stature, round face, short neck, obesity, mental retardation, brachydactyly and subcutaneous calcification is usually referred to as Albright's hereditary osteodystrophy (AHO) (Fitch, 1982). It can occur in subjects with pseudohypoparathyroidism or, without biochemical abnormalities, as pseudo-pseudohypoparathyroidism (Albright *et al.*, 1942; Albright *et al.*, 1952). A combination of hyperparathyroidism and AHO has so far not been documented, except for one case labelled pseudo-pseudohypohyperparathyroidism (Bronsky, 1970). The significance of this association is briefly discussed.

Case report

A 22 year old Japanese woman was admitted in January, 1978 with a 4 month history of intermittent epigastric discomfort and nausea, and for evaluation of hypercalcaemia and a raised serum alkaline phosphatase level. She was the product of a full-term pregnancy and uneventful delivery, with no known maternal illness during pregnancy. There was no history of tetany or paraesthesia. Family history included short stature, obesity and knuckles dimple sign in the paternal grandmother and patient's aunt.

Haruka Sasaki, M.D.; Nobutake Tsutsu, M.D.; Takashi Asano, M.D.; Takashi Yamamoto, M.D.; Masahiro Kikuchi, M.D.; Makoto Okumura, M.D.

Correspondence: Haruka Sasaki, First Department of Internal Medicine, Fukuoka University School of Medicine, Nanakuma, Jonan-ku, Fukuoka 814-01, Japan.

Accepted: 22 February 1984

She had specific features of AHO including short stature (44.5 kg, 144.5 cm), round face, short neck, mental retardation and short fourth finger and toes (Figure 1A and 1B). Chvostek and Trousseau signs were absent. The serum calcium was 2.9 ± 0.06 (s.e.) mmol/l (normal, 2.05–2.6) and serum phosphorus 0.96 ± 0.02 (s.e.) mmol/l (normal, 0.8–1.55). Serum ionized calcium was elevated to 3.25 mmol/l (normal, 2.10–2.35). The alkaline phosphatase, predominantly of bony origin, was 153 to 167 u/l (normal, 19–71). The immunoreactive parathyroid hormone (iPTH) levels were 1.54, 1.60 and 1.70 ng/ml on three different occasions in C-terminal assay (C-iPTH; normal range below 0.5 ng/ml) and 0.17 ng/ml in N-terminal assay (N-iPTH; normal range below 0.12 ng/ml). The serum 1,25-(OH)₂ vitamin D3 level was 86.5 pg/ml (normal, 20–60). A barium X-ray study of the gastrointestinal tract was normal. Plain films and drip infusion pyelogram showed no nephrocalcinosis. Chromosomes showed a normal 46-xx karyotype. Bone roentgenogram confirmed the presence of short fourth metacarpals and metatarsals (Figure 1). There were no detectable areas of calcification. The pituitary-adrenal axis and thyroid functions were within normal limits. The parathyroid scintigram and ultrasonic examinations were negative. The electroencephalogram showed moderate dysrhythmia and IQ was 60. Intravenous administration of 100 units of 1,34 human-PTH (Toyojoko Co., Tokyo, Japan) (Ellsworth–Howard's test) resulted in no change of urinary excretion of phosphorus, despite a 10-fold increase in the excretion of cyclic-AMP. The metabolic response and elevation of serum iPTH are considered to be compatible with a diagnosis of pseudo-hypoparathyroidism Type II (Drezner *et al.*, 1973).

Figure 1 X-ray views of hand (A) and photography of foot (B) demonstrating the shortening of the fourth metacarpal and metatarsal.

However, repeated determinations of serum calcium were high, while phosphorous levels were in the low normal range. Administration of prednisolone 40 mg/d for 8 days failed to correct the serum calcium and phosphorus levels. In addition, a rapid calcium infusion test (Goldsmith's method) did not alter the ratio of urinary phosphorus and creatinine excretion. Based on these observations and no evidence of other causes of hypercalcaemia, a diagnosis of primary hyperparathyroidism was made. As she declined operation, she was followed-up for about 4 y. The serum calcium levels remained elevated (2.75–3.05 mmol/l) and serum phosphorus levels were constantly low normal (0.65–0.87 mmol/l).

In August 1982, parathyroid exploration led to the finding of a single parathyroid tumour, the three remaining parathyroid glands showing macroscopic atrophy. The histology confirmed that this tumour was a parathyroid adenoma, predominantly of the chief cell type. Two weeks post-operatively, the serum calcium level had fallen to a low of 2.2 mmol/l, and the

serum phosphorus level was 1.06 mmol/l.

Seven months after surgery, she was re-admitted for evaluation. Serum calcium, phosphorus, alkaline-phosphatase and iPTH were normal. The phosphaturic response to PTH and a rapid calcium infusion test were normal.

Discussion

This case seems to be the second of hyperparathyroidism with parathyroid adenoma to be associated with AHO. AHO exists usually in two related metabolic forms, pseudohypoparathyroidism (PHP) and pseudo-pseudohypoparathyroidism (PPHP) (Albright *et al.*, 1942; Albright *et al.*, 1952; Fitch, 1982). PHP is a heterogeneous group of inheritable disorders characterized by a deficient end-organ response to action of parathyroid hormone (PTH). These patients usually have hypocalcaemia, hyperphosphataemia and increased levels of serum

iPTH. Patients with PPHP may be differentiated from those with PHP because they have normal serum calcium and phosphorus levels and normal phosphaturic and cyclic-AMP responses to PTH. The characteristic phenotype abnormalities (so-called AHO) are the only criteria for diagnosis of PPHP. However, it has been recognized for some time that PHP and PPHP can occur within the same family (Mann *et al.*, 1962). In addition, an instance of spontaneous conversion of PHP into PPHP in the same patient has been reported by Palubinskas & Davies (1959). Thus, PPHP is considered to be an incompletely expressed form of PHP. If our patient had been observed before the onset of hyperparathyroidism, she would probably have been diagnosed as a case of PPHP.

On the other hand, it is now recognized that some cases of PHP (Nusynowitz *et al.*, 1976; Winter &

Hughes, 1980) occur without AHO and that AHO may be present in PTH-deficient hypoparathyroidism (Moses *et al.*, 1974) and primary hyperparathyroidism such as in our patient. AHO is not a prerequisite for PHP, and its presence does not exclude PTH-deficient hypoparathyroidism and primary hyperparathyroidism.

Although the association between the two conditions in our case may be coincidental, we suggest that the spectrum of AHO syndromes is wider than generally appreciated.

Acknowledgements

We thank Dr Shiro Noguchi (Noguchi Hospital, Beppu, Japan) for performing the operation and Ms M. Ohara (Kyushu University) for comments on the manuscript.

References

- ALBRIGHT, F., BURNETT, C.H., SMITH, H. & PARSON, W. (1942). Pseudo-hypoparathyroidism - An example of 'Seabright-Bantam Syndrome'. *Endocrinology*, **30**, 922.
- ALBRIGHT, F., FORBES, A.P. & HENNEMAN, P.H. (1952). Pseudo-pseudohypoparathyroidism. *Transactions of the Association of American Physicians*, **65**, 337.
- BRONSKY, D. (1970). Hyperparathyroidism with Albright's osteodystrophy: Case report and a proposed new classification of parathyroidism disease. *Journal of Clinical Endocrinology and Metabolism*, **31**, 271.
- DREZNER, M., NEELAN, F.A. & LEBOVITZ, H.E. (1973). Pseudohypoparathyroidism Type II: An possible defect in the reception of the cyclic AMP signal. *New England Journal of Medicine*, **289**, 1059.
- FITCH, N. (1982). Albright's hereditary osteodystrophy: a review. *American Journal of Medical Genetics*, **11**, 11.
- MANN, J.B., ALTERMAN, S. & HILLS, A.G. (1962). Albright's hereditary osteodystrophy comprising pseudohypoparathyroidism and pseudopseudohypoparathyroidism. *Annals of Internal Medicine*, **36**, 315.
- MOSES, A.M., RAO, K.J., COULSON, R. & MILLER, M. (1974). Parathyroid hormone deficiency with Albright's hereditary osteodystrophy. *Journal of Clinical Endocrinology and Metabolism*, **39**, 496.
- NUSYNOWITZ, M.L., FRAME, B. & KOLB, F.O. (1976). The spectrum of the hypoparathyroidism states: A classification based on physiological principles. *Medicine (Baltimore)*, **55**, 105.
- PALUBINSKAS, A.J. & DAVIES, H. (1959). Calcification of the basal ganglia of the brain. *American Journal of Roentgenology*, **82**, 806.
- WINTER, J.S.D. & HUGHES, I.A. (1980). Pseudohypoparathyroidism without somatic anomalies. *Canadian Medical Association Journal*, **123**, 26.